A Placebo-Controlled Double Blind Trial of Etanercept for the Cancer Anorexia/Weight Loss Syndrome

*Results From N00C1 From The North Central Cancer Treatment Group*

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**BACKGROUND.** Tumor necrosis factor-a (TNF-a) is a putative mediator of the cancer anorexia/weight loss syndrome. The current study was designed to determine whether etanercept (a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75-kilodalton TNF receptor linked to the Fc portion of human immunoglobulin [Ig] G1) could palliate this syndrome.

**METHODS.** A total of 63 evaluable patients were randomly assigned to receive either etanercept at a dose of 25 mg subcutaneously twice weekly versus a comparably administered placebo. All patients had an incurable malignancy, acknowledged loss of weight and/or appetite as a concern, and reported a weight loss of >2.27 kg over 2 months and/or a daily intake of <20 calories/kg body weight.

**RESULTS.** Over time, weight gain was found to be minimal in both treatment arms; no patient gained >= 10% of their baseline weight. Previously validated appetite questionnaires revealed negligible improvements in both treatment arms. The median survival was also comparable (175 days vs 148 days in etanercept-treated and placebo-exposed patients, respectively; P 5.82). Finally, preliminary data regarding adverse events demonstrated that patients treated with etanercept had higher rates of neurotoxicity (29% vs 0%) but lower rates of anemia (0% vs 19%) and thrombocytopenia (0% vs 14%). Infection rates were negligible in both groups. Genotyping for TNF-a-238 and TNF-a-308 polymorphisms revealed no clinical significance for these genotypes, except for a preliminary association between presence of the 2238 G/A genotype and relatively less favourable survival.

**CONCLUSIONS.** Etanercept, as prescribed in the current trial, does not appear to palliate the cancer anorexia/weight loss syndrome in patients with advanced disease.

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**Strengths:**
- Intriguing example of rational drug design/use, using a commercially available preparation.
- Commented on good effect in mouse models.
- Relevant to our sample population:
- Adults with tissue proven malignancy, with documented weight loss, where the patient perceived weight loss as a problem.
- Randomized, double-blind, placebo controlled.
Weaknesses:
- Small sample size of 63 patients.
- No comment on allocation concealment.
- High drop-out rate.
  - No mention of how these drop-outs were handled in the statistical analysis.
  - No mention of intention-to-treat.
- Weight gain of 10% was judged to be a “treatment success.” Analysis was using 2-tailed test. Why did they use discrete analysis techniques on what is normally considered continuous data?
- Results not able to reach statistical significance.

Relevance to Palliative Care: This study was unable to show an improvement in weight in anorexic/cachectic cancer patients treated with etanercept. The study is an interesting exploration of the anorexic process in a clinical population. However, the mechanism for weight loss is multifactorial and TNFa is not the only cytokine involved. On a more practical note, how accessible would monoclonal antibodies be for our population, were they to show an effect? The syndrome continues to be a common problem for which there are limited treatment options.